IN THE UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF CALIFORNIA

CARNEGIE MELLON UNIVERSITY, et al.,

Plaintiffs,

v.

HOFFMAN-LA ROCHE, INC., et al.,

Defendants.

/

No. C 95-3524 SI
No. C 01-0415 SI

FINDINGS OF FACT AND CONCLUSIONS OF LAW RE: DEFENSES OF INEQUITABLE CONDUCT

BACKGROUND

The first action (No. C 95-3524 SI): Plaintiffs Carnegie Mellon University and Three Rivers Biologicals, Inc. filed suit against several defendants alleging infringement of U.S. Patent No. 4,767,708 ('708 patent) and U.S. Patent No. 5,126,270 ('270 patent), both entitled "Enzyme Amplification and Purification." The patents-in-suit are directed to (1) recombinant plasmids for the controlled expression of an enzyme identified in the '708 patent as "DNA polymerase I," (2) processes related to the construction of such plasmids, and (3) processes related to the culturing of host cells containing such plasmids. The patents derive from the same original application. The Patent and Trademark Office ("PTO") issued the '708 patent from a "parent" application, No. 06/638, 638 ('638 application) filed on August 7, 1984, and the '270 patent from a "continuation" application filed on November 5, 1987.

On May 12, 1999, the Court granted defendants' motion for summary judgment in the first action, finding that the asserted claims of the '708 patent were not infringed by their accused manufacturing activities. In July 1999, defendants moved for summary judgment that certain claims of the '270 patent were invalid under the written description requirement. The Court found the *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473 (Fed. Cir. 1998), argument persuasive and held that the

'270 patent was invalid because it failed to incorporate lethality, which was an essential feature of the claimed invention. Order (Aug. 19, 1999) 10-11. On June 27, 2001, the Court granted defendants' motion for summary judgment, finding that the asserted claims of the '708 patent are invalid under *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997).

The second action (No. C 01-0415 SI): On January 24, 2001, plaintiffs filed a second suit against defendants, this time alleging infringement of the '745 patent, a continuation of the '270 patent. On September 23, 2003, the Court granted summary judgment for the defendants in that action, finding that the challenged claims of the '745 patent are also invalid under *Eli Lilly*.

The bench trial: In both of these related actions, defendants also asserted that plaintiffs committed inequitable conduct in connection with prosecution of each of the asserted patents ('708, '270, and '745) and that the patents are therefore unenforceable. Defendants' motion for summary judgment on the inequitable conduct defenses was denied in January, 2005. A bench trial on inequitable conduct was conducted from August 1 to August 4, 2005. This Order constitutes the Court's findings of fact and conclusions of law in accordance with Federal Rule of Civil Procedure 52(a).

Defendants presented three theories of inequitable conduct at trial: (1) that during prosecution of the latest of the three patents, the '745 patent, plaintiffs intentionally withheld from the PTO a material declaration by Dr. Robert Bambara, defendants' expert in the first action; (2) that during prosecution of the first two patents at issue, the '708 and '270 patents, plaintiffs submitted to the PTO a materially misleading declaration (the 1990 Minkley Declaration) with the specific intent to deceive the PTO; and (3) that during prosecution of the '708 and '270 patents, plaintiffs intentionally withheld two allegedly material references (the "Murray & Kelley" and "Remaut" publications) with the intent of deceiving the PTO into allowing claims of the patents.

Proof of inequitable conduct must be by clear and convincing evidence. As is set out more fully below, the Court finds that defendants have not presented clear and convincing evidence to support any of their theories of inequitable conduct and the Court concludes that none of the patents is unenforceable on that account.

FINDINGS OF FACT

The Litigation, Parties And Patents In Suit

1. U.S. Patent No. 4,767,708 ("the '708 Patent") issued on August 30, 1988 to Carnegie Mellon University ("Carnegie Mellon") from Application Serial No. 06/638,638 ("the '638 Application"), filed on August 7, 1984. The '708 Patent, by a Certificate of Correction, names Edwin G. Minkley, Jr. as sole inventor. [Undisputed Finding of Fact ("UF") No. 1[1]]

2. U.S. Patent No. 5,126,270 ("the '270 Patent") issued on June 30, 1992 to Carnegie Mellon and is a continuation of the '708 Patent. The '270 Patent names Edwin G. Minkley, Jr. as sole inventor. [UF No. 2]

3. U.S. Patent No. 6,017,745 ("the '745 Patent") issued on January 25, 2000 to Carnegie Mellon and is a continuation of the '270 Patent. The '745 Patent names Edwin G. Minkley, Jr. as sole inventor. [UF No. 3]

4. Carnegie Mellon and Three Rivers Biologicals, Inc. (collectively, "plaintiffs") filed suit on August 30, 1994 for alleged infringement of the '708 and '270 patents in an action initially commenced in the Western District of Pennsylvania and subsequently transferred at the Defendants' request to this Court where it was designated case number C 95-03524 SI. [UF No. 4]

5. Edwin G. Minkley, Jr. ("Dr. Minkley") is, and at all relevant times has been, the President and one-half share owner of Three Rivers Biologicals, Inc. [UF No. 5]

7. Carnegie Mellon University filed suit on January 24, 2001 for alleged infringement of the '745 Patent in an action that was designated case number C 01-0415 SI ("the second action"). [UF No. 6]

8. On May 12, 1999, the Court granted defendants' summary judgement motion that the asserted claims of the '708 Patent are not infringed by their accused manufacturing activities. On August 19, 1999, the Court granted defendants' summary judgment motion that the asserted claims of

[1]Most of the underlying facts in this case are undisputed and are identified as such by reference to the parties' proposed Undisputed Findings of Fact. The parties do dispute what inferences should be drawn from those facts.

the '270 Patent are invalid under *Gentry Gallery, Inc., v. Berkline Corp.*, 134 F.3d 1473 (Fed. Cir. 1998). On June 27, 2001, the Court granted defendants' summary judgement motion that the asserted claims of the '708 Patent are invalid under *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997). On September 29, 2003, the Court granted defendants' summary judgment motion that the challenged claims of the '745 Patent are invalid under *Eli Lilly*. On January 14, 2005, the court heard argument on, and denied, defendant's motion for summary judgment of inequitable conduct. [UF No. 7]

9. The two actions have been consolidated for resolution of the issue of inequitable conduct. After addition and dismissal of various parties, the remaining defendants in the First Action are Hoffmann-La Roche Inc., Roche Molecular Systems, Inc., Roche Diagnostic Systems, Inc., Roche Biomedical Laboratories, Inc., The Perkin-Elmer Corporation and Laboratory Corporation of America Holdings, and the remaining defendants in the Second Action are Hoffmann-La Roche Inc., Roche Molecular Systems, Inc., Roche Diagnostics Corporation, Laboratory Corporation of America, and Applera Corporation (collectively, "defendants"). [UF No. 8]

The Science

10. A gene may be defined as a region of DNA that contains information that a cell uses to make a particular protein. [UF No. 71] Expression is the name given to the process by which a cell uses the information in a gene to make the corresponding protein. [UF No. 72]

11. Expression includes two steps called transcription and translation. [UF No. 73] Transcription is the process by which the information in a gene is copied into a nucleic acid called "messenger RNA" (mRNA). [UF No. 74] Translation is the process in which the cell, using the information in the mRNA, assembles amino acids in the correct sequence to make the corresponding protein. [UF No. 75]

12. A particular gene in the *E. coli* bacterium, called the "*polA*" gene, has been the subject of scientific study since at least the 1970s. [UF No. 76] The *E. coli polA* gene encodes a protein called "*E. coli* DNA polymerase I." [UF No. 77] The wild-type *E. coli polA* gene includes two parts: (1) the structural gene (or "gene coding region") and (2) the promoter. [UF No. 78] The "structural

gene" (or "gene coding region") of the *E. coli polA* gene carries the encoded genetic information that specifies the sequence of amino acids that must be assembled to make the *E. coli* DNA polymerase I protein. [UF No. 79] The "promoter" is a region of a gene that is required for transcription to begin. [UF No. 80]

13. Certain promoters, called "regulatable promoters," may be turned off by a "repressor" or turned on by an "inducer." [UF No. 81] Promoters are composed of DNA. [UF No. 82] A repressor is a protein, not DNA. [UF No. 83] An inducer is typically, but not always, a small molecule and is not DNA. [UF No. 84]

14. As used by molecular biologists, the term inducer is not used to describe a promoter, but rather to describe a stimulus, typically a small molecule, that activates a promoter. [UF No. 85] The lambda p_L promoter is not a repressor or an inducer. [UF No. 86, 87]

15. Expression may be regulated by controlling the level of transcription from the promoter. [UF No. 88]

16. A "vector" is a type of DNA that can be used for introducing and maintaining a foreign gene in a host cell. [UF No. 89] Bacteriophages ("phages") and plasmids are two different types of vectors. [UF No. 90] A plasmid is a small circular loop of extrachromosomal DNA that can replicate within a bacterial host cell, separate from the chromosome. A "multicopy" or "relaxed" plasmid multiplies within the host cell until the host cell contains at least 10 copies of the plasmid. With low copy number plasmids, the host cell contains fewer than 10 copies per cell. [UF No. 91]

17. In 1977, Professor Noreen Murray and her colleagues published a paper in which they reported cloning the wild-type *E. coli polA* gene into a phage vector. Kelley *et al., Proc. Natl. Acad. Sci. USA*, vol. 74, ¶. 5632-5636 (1977) ("the 1977 Kelley Publication"). [UF No. 92] The 1977 Kelley Publication reported experiments in which the authors transferred the wild-type *E. coli polA* gene, including its promoter, into a phage that was then introduced into bacterial host cells. The host cells containing this phage with its *E. coli polA* gene produced elevated levels of DNA polymerase I. [UF No. 93]

18. The 1977 Kelley Publication reported a toxicity problem that prevented the wild-type *E. coli polA* gene from being propagated in a high copy number plasmid. [UF No. 94] Host cells

containing a high copy number plasmid comprising the wild-type *E. coli polA* gene would contain many copies of that gene. [UF No. 95] When host cells contain high copy numbers of the wild-type *E. coli polA* gene, they make high levels of the protein *E. coli* DNA polymerase I.

19. The 1977 Kelley Publication suggested that elevated quantities of *E. coli* DNA polymerase I were detrimental to the host cell.:

> It is probable that overproduction of polymerase I resulting from multiple copies of the *polA* gene and its promoter is detrimental to the cell. (1977 Kelley Publication, page 5635, left column).

Ex. 21.

20. The patents-in-suit set forth a solution to the toxicity problem identified by the 1977 Kelley Publication: damaging or removing the natural *polA* promoter and placing the *polA* gene coding region under control of a regulatable promoter in a multicopy plasmid. *See* Exs. 1-3.

21. The patents-in-suit describe a plasmid called "pMP5" in which expression of the *E. coli polA* gene coding region is controlled by a regulatable promoter called the "lambda p_L promoter." [UF No. 96]

Alleged Inequitable Conduct re '745 Patent Prosecution:
The Bambara Declaration

22. On July 9, 1999, in the first action, the defendants filed a motion for summary judgment of invalidity, challenging certain claims of the '270 Patent as invalid for lack of written description under two theories: one theory based on the Federal Circuit's ruling in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), and the other based on the Federal Circuit's ruling in *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473 (Fed. Cir. 1998). [UF No. 9]

23. In support of the '270 summary judgment motion, defendants submitted a declaration, dated July 2, 1999, by Professor Robert A. Bambara ("the Bambara Declaration"; Trial Exhibit 12). [UF No. 10] The Bambara Declaration set forth factual evidence in support of defendants' challenge under *Eli Lilly* that the claims were not supported by an adequate written description, and also set forth factual evidence in support of defendants' challenge under *Gentry*. *See* Ex. 12.

24. The Bambara Declaration stated the following facts relevant to the *Eli Lilly* issue: (1) *polA* is not a single gene, but rather a large class of distinct genes that differ from one bacterial species to another, encoding a family of enzymes that likewise differ from one bacterial species to another; (2) in 1984, when the '638 Application was filed, only three members of the class of *polA* genes had been cloned; and (3) the '638 Application fails to show that the applicants possessed any member of this class of genes except the *E. coli polA* gene. Based on these facts, the Bambara Declaration also asserted the following opinion relevant to the *Eli Lilly* issue: without other *polA* genes the inventors could not construct plasmids for expressing nick-translating enzymes or polymerase enzymes of bacteria other than *E. coli*. *See* Bambara Declaration ¶¶ 28-31 (Ex. 12).

25. Most of the facts contained in this portion of the Bambara Declaration were known by 1984 to those skilled in the art. It was known in the art by 1984 that there were thousands of bacterial species, that "*polA*" was not a single gene for all bacterial species but rather referred to a large family of genes that differed from one bacterial species to another, and that *polA* genes encode a very large family of enzymes that differ from one bacterial species to another. [UF No. 33, 37, 38, 39]

26. By 1980, and by 1984, three bacterial *polA* genes had been reported as being cloned. [UF No. 31, 32]

27. A publication by Struhl & Davis (*J. Molecular Biology*, vol. 141, 343-368 (1980) ("the Struhl & Davis Publication") was submitted to the PTO by plaintiffs' patent counsel during the prosecution of the '745 Patent. [UF No. 34] The Struhl & Davis Publication reports the cloning of the *polA* genes from *K. aerogenes* and *K. pneumoniae*. [UF No. 35] The Struhl & Davis Publication does not address how many *polA* genes had been cloned by 1984. [UF No. 36]

28. During briefing and argument of the '270 summary judgment motion, the plaintiffs were represented by the Reed Smith law firm. Frederick H. Colen, a Reed Smith partner, represented the plaintiffs in opposing the '270 summary judgment motion and attended the oral argument on August 13, 1999. Ex. 14 at 5:3. [UF No.11] At the August 13, 1999 oral argument on the '270 summary judgment motion, defendants referred to and relied on the Bambara Declaration in support of their *Eli Lilly* invalidity challenge. Ex. 14 at 20:11-14; 19:15-18.

29. On August 19, 1999 the Court issued an Order holding claims 1-2, 11-12, 14-15,

17-18, 20-21, 23-24, 26-27, 29-30 and 32-36 of the '270 Patent invalid under *Gentry* for lack of a supporting written description of the claimed subject matter ("the '270 Invalidity Order"). *Carnegie Mellon University v. Hoffmann-La Roche Inc.*, 1999 WL 33298545 at *3 (N.D.Cal. Aug 19, 1999). [UF No. 12] In the '270 Invalidity Order, the Court found it unnecessary to reach the defendants' *Eli Lilly* challenge. [UF No. 13]

30. The '270 Invalidity Order cites the Bambara Declaration in connection with the *Gentry* issue, but does not refer to Dr. Bambara's factual evidence concerning invalidity under *Eli Lilly*, nor does it mention that the Bambara Declaration sets forth factual evidence concerning invalidity under *Eli Lilly*. *See id.*, 1999 WL 33298545 at *3. The '270 Invalidity Order did, however, summarize defendants' argument as to the *Eli Lilly* challenge, stating:

> Second, defendants argue that the specification does not meet the governing standard for DNA inventions because the specification describes only one plasmid, containing a DNA sequence derived from one bacterial species, that encodes a single enzyme. Defendants argue that because the claims encompass plasmids that contain any DNA sequence, derived from any bacterial species, that encodes any enzyme possessing the described enzyme activities, the claims are not supported by the specification. *See Lilly*, 119 F.3d at 1568-69.

Id.

31. As of August 19, 1999, when this Court's Invalidity Order issued concerning the '270 patent, the application that became the '745 patent was still pending before the PTO: the claims of the '745 patent had been allowed but the '745 Patent had not yet issued. [UF No. 14]

32. Reed Smith attorneys, including Frederick H. Colen, were of record in the application that issued as the '745 Patent. [UF No. 28] Frederick H. Colen signed and submitted certain papers to the PTO in connection with the prosecution of the '745 Patent. [UF No. 29] During prosecution of the '745 Patent, Carnegie Mellon's patent counsel, including Frederick H. Colen, were aware of the Bambara Declaration. [UF No. 30]

33. After this Court issued the '270 Invalidity Order, Carnegie Mellon's patent counsel requested that the PTO confirm the patentability of the allowed claims of the '745 patent in light of *Eli Lilly* and *Gentry*. [UF No. 15]

34. On October 6, 1999, the Examiner in charge of the prosecution of the '745 patent

conducted an interview with Carnegie Mellon's counsel at which they discussed the first action and the Federal Circuit's rulings in *Eli Lilly* and *Gentry* and at which the Examiner confirmed patentability of the '745 patent's allowed claims in light of *Eli Lilly* and *Gentry*. [UF No. 16] Prior to that meeting, in July, 1999, Carnegie Mellon's counsel had submitted to the PTO a Communication transmitting copies of the following pleadings and orders regarding the First Action: (i) the Second Amended Complaint; (ii) Roche Defendants' Answer to the Second Amended Complaint; (iii) Defendants Chiron Corporation's and Cetus Oncology Corporation's Corrected Answer to plaintiffs' Second Amended Complaint; (iv) the Court's Order dated March 31, 1997 Granting and Denying in Part Roche and Chiron Defendants' Requested Claim Construction and Granting and Denying in Part Plaintiffs' Requested Claim Construction; (v) the Court's Order dated February 2, 1998 Denying Defendants' Motion for Summary Judgment That Claims 1-19, 22-40 and 43-45 of the '708 Patent Are Invalid Under 35 U.S.C. § 112; and (vi) the Court's Order dated May 12, 1999 Granting In Part And Denying In Part Defendants' Motions To Exclude The Testimony Of Plaintiffs' Experts And Granting Defendants' Motions For Summary Judgment [as to Non-Infringement of the '708 Patent]. [UF No. 17]

35. At the October 6, 1999 meeting, Carnegie Mellon's counsel re-submitted to the PTO copies of the July 30, 1999 Communication along with the following additional materials from the first action: (i) the August 19, 1999 Order Granting Defendants' Motion for Summary Judgment on Invalidity and Denying Plaintiffs' Motion for Summary Judgment as Moot (i.e., the '270 Invalidity Order); (ii) Expedited Motion Requesting Leave to File A Motion for Reconsideration of this Court's August 19, 1999 Summary Judgment Order; (iii) Chiron Defendants' Joinder in Roche Defendants' Opposition to Plaintiffs' Expedited Motion Requesting Leave to File a Motion for Reconsideration of this Court's August 19, 1999 Summary Judgment Order; (iv) Roche Defendants' Opposition to Plaintiffs' Expedited Motion Requesting Leave to Move for Reconsideration of this Courts' August 19, 1999 Summary Judgment Order; and (v) the Court Docket List, current as of September 13, 1999. [UF No. 18]

36. The Court Docket List as submitted to the PTO by Carnegie Mellon's counsel on October 6, 1999, lists the Bambara Declaration as Docket Entry No. 290. [UF No. 19] However, at no time during prosecution of the '745 Patent did Carnegie Mellon's counsel provide the PTO with

a copy of the Bambara Declaration, or with copies of the parties' briefs filed on July 9, July 23, July 30, or August 6, 1999 concerning the '270 summary judgment motion. [UF No. 20, 21]

37. On January 25, 2000, the PTO issued the '745 Patent. [UF No. 23]

38. On January 26, 2000, the plaintiffs filed a request for leave to move for reconsideration of the '270 Invalidity Order. In that motion, plaintiffs admitted that the '745 Patent "has claims that are similar in pertinent part to the claims of the '270 Patent and that the written description of the '745 Patent and the '270 Patent are in relevant part identical." [UF No. 24]

39. On January 24, 2001, Carnegie Mellon University commenced the second action, in which it asserted the '745 patent against the defendants. [UF No. 25] On September 28, 2001, the defendants in the second action filed a motion for summary judgment of invalidity ("the '745 summary judgment motion"), challenging certain claims of the '745 patent as invalid for lack of written description under both *Eli Lilly* and *Gentry*. In support of this motion, defendants submitted a copy of the Bambara Declaration, which Professor Bambara had readopted for purposes of the second action. [UF No. 26]

40. On September 29, 2003, after briefing and argument, this Court held claims 1-3, 12-14, 23-28 and 30-33 of the '745 Patent invalid under *Eli Lilly* for lack of written description ("the '745 Invalidity Order"). In this Order, the Court relied on the factual evidence set forth in the Bambara Declaration. The Court further found that the PTO was not presented, during its consideration of the '745 patent, with the expert testimony of Professor Bambara. On that basis, the Court held that it owed no deference to the Examiner's decision to issue the '745 Patent. [UF No. 27]

41. Plaintiff's expert, Ronald Bjorge, credibly testified that while the PTO is interested in receiving as much material litigation information as possible, "if you submit too much information, it tends to get buried, and then the examiner is not helped either." Reporter's Transcript ("RT") at 365-366. "Trying to achieve the balance of just the right amount is the balancing act that the office and the attorneys or the applicants must try to achieve." RT at 366.

42. The Bambara Declaration was material to patentability of the '745 patent, though not highly so. It contained the opinion of one expert, created for a case with a large record. The Court's '270 Patent invalidity order, which plaintiffs provided to the Examiner, summarized defendants'

argument regarding *Eli Lilly*. Even without the Bambara Declaration, therefore, the Examiner was aware of the argument that the Bambara Declaration supported.

43. During prosecution of the '745 patent, Carnegie Mellon's patent counsel, including Frederick H. Colen, understood the relevance of the Bambara Declaration to patentability under *Eli Lilly* of the claims of the '745 Patent. However, defendants did not present clear and convincing evidence that Carnegie Mellon's patent counsel deliberately withheld the Bambara Declaration in order to secure issuance of the '745 Patent. Because the Declaration was not highly material, the Court will not infer intent to deceive the PTO. Furthermore, the opinions and facts contained in the Declaration were summarized in the Court's '270 Invalidity Order, which plaintiffs presented to the Examiner.

Alleged Inequitable Conduct re: the '708 and '270 Patents:
The Minkley Declaration And The March 15, 1990 Amendment

44. The application which issued as the '708 patent was filed on August 7, 1984. [UF No. 40] During prosecution of the '708 patent, in the first office action dated July 1, 1986, the Examiner cited Minkley *et al., J. Biol. Chem*. vol. 259, ¶. 10386-10392 (1984) ("the 1984 Minkley Publication"), Trial Exhibit 24, as being "of interest because it helps clarify the issues of the instant disclosure." [UF No. 42].

45. Later during prosecution of the '708 Patent, in a response submitted on November 5, 1987, the Applicants amended the claims to recite (for the first time) the limitation "… in a suitable bacterial or yeast host system." (*See, e.g.* Claims 1, 25, and 46, Page 2 of Response dated November 5, 1987.) [UF No. 51] Applicants resubmitted these remarks in a further Response dated December 28, 1987. Thereafter, Examiner Mays issued a Notice of Allowability on January 29, 1988. [UF No. 52]

46. The application that issued as the '270 patent was filed on November 5, 1987. The Applicants filed a preliminary amendment in which claims directed to processes were amended to recite a "host strain of cells" while other claims directed to a cell culture were amended to recite a "suitable bacterial or yeast host system." (*See, e.g.*, Claims 41 and 46, respectively, Preliminary Amendment dated April 29, 1988.). [UF No. 53]

47. In an Office Action dated, October 3, 1989, during prosecution of the '270 patent, Examiner Mays rejected certain claims as obvious over a publication by Spanos & Sedgwick, published in *Current Genetics*, vol. 8, ¶. 333-340 (1984) ("the Spanos Publication"), Trial Exhibit 20, in combination with the 1984 Minkley Publication and Joyce & Grindley, *Proc. Natl. Acad. Sci. USA*, vol. 80 pp.1830-1834 (1983). (Page 12, Office Action dated October 3, 1989). [UF No. 54]

48. The Spanos Publication reports experiments in both bacterial and yeast host systems, in which the authors placed a recombinant plasmid encoding *E. coli* DNA polymerase I in a host system, allowed the host system to reproduce, and obtained *E. coli* DNA polymerase I enzyme reproduced from the host system. *See* Ex. 20. [UF No. 55, 56]

49. *E. coli* DNA polymerase I is an enzyme that possesses Nick-translation activity. [UF No. 57]

50. On March 9, 1990, Dr. Minkley executed a declaration ("the Minkley Declaration") in which he swore:

> At least as early as December 14, 1983, I had placed a recombinant plasmid providing for Nick-translation activity in a bacterial or yeast host system. Next, I allowed such a bacterial or yeast host system to reproduce. I then obtained an enzyme for Nick-translation activity from the host systems that reproduced. An article, see E.G. Minkley et al. J. Biol. Chem. 259(16) 10386 (1984), copy attached, describing the same was submitted for publication on December 14, 1983. This publication evidences the conception and reduction to practice of the claimed invention at least as early as December 14, 1983, which is before the Spanos et al. reference was published. (Minkley Declaration, page 2).

[UF No. 58]

51. The Minkley article referenced in the Declaration describes Minkley's work with the *E. Coli* bacterial host system, exclusively. Ex. 24.

52. In executing the Minkley Declaration, Dr. Minkley was aware of his duty of candor, which he acknowledged in the declaration as follows:

> I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements in [sic] the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

[UF No. 59]

53. On March 15, 1990, Dr. Minkley and his counsel submitted the Minkley Declaration to the PTO together with an Amendment that stated in part:

> A declaration under §1.131 is included herewith which states that Applicant conceived and reduced to practice the claimed invention at least as early as December 14, 1983, which is before the publication date of the Spanos et al. reference (a copy of the Spanos reference is enclosed). The publication date of Spanos et al. is on or about June 26, 1984, which is to the best of applicant's knowledge when the publication was received by Carnegie-Mellon University, Mellon Institute. Accordingly, any rejection based on the Spanos et al. reference should be removed. (Page 16, Amendment dated March 15, 1990).

[UF No. 60]

54. Dr. Minkley had never placed a recombinant plasmid providing for Nick-translation activity in a yeast host system, nor had he ever obtained an enzyme for Nick-translation activity from a yeast host system. [UF No. 61, 62] Dr. Minkley never performed experiments with a plasmid providing for Nick-translation activity in a yeast host system. [UF No. 63]

55. Dr. Minkley reviewed and approved the March 15, 1990 Amendment prior to its submission to the PTO. [UF No. 64] The text of the 1990 Minkley Declaration, which was filed under 37 C.F.R. § 1.131, shows that it was submitted to antedate Spanos and Sedgwick, and the Declaration and the March 15, 1990 Amendment were in response to the October 3, 1989 Office Action. [UF No. 65, 66]

56. The language of the 1990 Minkley Declaration tracks the language of the '270 patent claims that were then pending; "recombinant plasmid," "Nick–translation activity," and "bacterial or yeast host system" were all verbatim limitations found in the pending claims. (Page 1 of the Response dated March 15, 1990.) By tracking the pending claim language, the 1990 Minkley Declaration declares that the "subject matter of the rejected claim" was reduced to practice prior to the publication of Spanos & Sedgwick. [UF No. 67]

57. The 1990 Minkley Declaration and the pending claims mirrored the claim language ("bacterial or yeast host system") that had previously been accepted by Examiner Mays during prosecution of the '708 patent, but which Examiner Mays rejected in the October 3, 1989 Office Action

on the '270 patent. The March 15, 1990 Response that accompanied the 1990 Minkley Declaration referred explicitly to the parent application:

> Claims 41-44 and 67-81 are rejected under 35 U.S.C. §112, first paragraph, as the disclosure is enabling only for claims limited to a culture of bacterial cells of E. coli, plasmids replicable and expressible therein and methods for employing the same. See MPEP §706.03(n) and 706.03(z). In general, applicants refer to the parent application, which is not patented and to the claims therein which speak to bacterial and yeast host systems. Applicants now enter into the record essentially the same argument that was presented during the prosecution of the parent application in order to persuade the examiner that the disclosure is enabling for bacterial and yeast in general, and not limited to just bacterial cells of E. coli, etc. Accordingly for these reasons, as well as the following reasons, the application is enabling for bacterial and yeast host systems, and the claims have been amended accordingly. (Page 6, March 15, 1990 Amendment.)

[UF No. 68]

58. In the next substantive Office Action that issued on July 23, 1990, Examiner Lebovitz abandoned the 35 U.S.C. §103 obviousness rejection that was based on Spanos & Sedgwick, stating, "Receipt of the Declaration filed under § 1.131 is acknowldged [sic] and the claimed priority is accepted." (Page 2, Office Action dated July 23, 1990.) Thus, the 1990 Minkley Declaration allowed the applicants to antedate Spanos & Sedgwick – the exact purpose to which it was drawn. [UF No. 69]

59. The enablement rejection under § 112 regarding the bacterial host system was maintained by the Examiner. The Examiner stated that the "specification does not establish that the instant vector would be functionally active in yeast or other bacterial strains." (Page 4, Office Action dated July 23, 1990.) [UF No. 70]. Thus, the Examiner was not convinced by the Minkley Declaration, or any other representations, that Dr. Minkley had performed experiments in both bacterial *and* yeast host systems. Minkley's failure to explicitly indicate in the Declaration that he had only performed experiments on bacterial hosts was immaterial.

60. There is no clear and convincing evidence that the Minkley Declaration and the March 15, 1990 Amendment were intended to convince the examiner that Dr. Minkley had performed experiments in both bacterial and yeast host systems. To the contrary, the Minkley Declaration specifically cites to the 1984 Minkley Publication, which describes in detail the work done by Minkley – work done only in an *E. Coli* bacterial host system. This is evidence that Minkley did not intend to

mislead the Examiner.

61. There is no clear and convincing evidence that in submitting the Minkley Declaration and the March 15, 1990 Amendment, Dr. Minkley and his counsel deliberately submitted a material false statement in order to persuade the Examiner to withdraw the rejection based on the Spanos Publication.

Alleged Inequitable Conduct re: the '708 and '270 Patents:
The Remaut Publication

62. In 1981, three years before the '638 Application was filed, Remaut and his colleagues published a scientific paper describing plasmids containing the lambda p_L promoter, a regulatable promoter. Remaut *et al*., *Gene* vol. 15 ¶. 81-93 (1981) ("the 1981 Remaut Publication"). [UF No. 97, 98]. Ex. 22.

63. The 1981 Remaut Publication describes plasmids that provide the ability to regulate the expression of gene coding regions. It does not directly report work with any *PolA* gene, does not report placing the *E. coli polA* gene coding region onto a multicopy plasmid, and does not report the removal of the natural promoter from the *E. coli polA* gene coding region. [UF No. 100, 101, 102]

64. In discussion, the 1981 Remaut Publication stated:

> The ability to control transcription may be a prerequisite for cloning of genes whose continuous expression is detrimental to the cell (either the protein may be toxic or interfering with normal cell metabolism, or high-level expression of an innocuous protein may constitute an intolerable load). This may explain, for example, why Kelley *et al*. (1977) were unable to clone the gene for polymerase I on a relaxed plasmid whereas a transducing phage carrying this gene was perfectly viable.

Ex. 22, 1981 Remaut Publication, page 90, right column.

65. Plaintiffs' expert, Dr. Ronald Davis, credibly and convincingly testified that the Remaut Publication offers no more than a guess (*i.e.*, "the ability to control transcription may be a prerequisite") as a potential solution to the lethality problem described in Kelley et al. (1977). RT at 391, 401. The Remaut Publication provides no procedures or plasmid constructs by which one of skill in the art could accomplish the "ability to control transcription." RT at 389-391, 399. One of the

reasons that the Remaut Publication cannot offer a working solution to the problem of placing the *polA* gene coding region onto a multicopy plasmid is that the authors did not work with *polA* at all, nor did they report work with any toxic gene product. RT at 237-238.

66. Dr. Davis credibly testified that the Remaut Publication offers no teaching to the skilled practitioner regarding the problem of placing the polA gene coding region onto a multicopy plasmid. RT at 389-391, 399; Ex. 43 ¶ 12. Nor does the Remaut Publication recognize the importance of reducing the activity of the natural promoter -- an important feature of the invention claimed in the patents in suit.[2] Ex. 43 ¶ 15. Finally, Remaut does not discuss or teach manipulating the natural promoter of the *polA* gene independent of the gene coding region. *Id.* ¶ 16.

67. Dr. Minkley cited portions of the 1981 Remaut Publication as a reference in the scientific publication in which he reported the work on which the patents-in-suit are based: Minkley *et al., J. Biol. Chem.* vol. 259, ¶. 10386-10392 (1984) ("the 1984 Minkley Publication"). [UF No. 103]

68. Dr. Minkley testified credibly that he could not recall reading the entire Remaut article in the 1983-1984 time period. He remembers only reading, and using, two portions of the Remaut article. Neither of those portions relates to controlling transcription. *See* RT at 229-234.

69. The 1981 Remaut Publication was never cited to the PTO in an Information Disclosure Statement or given to the PTO in connection with the prosecution of the '708 or '270 patents. [UF No. 104, 105] The prosecution histories of the '708 and '270 patents do not include a copy of the Publication, nor is it mentioned in the specification or the "References Cited" sections of the patents-in-suit. [UF No. 106, 107, 108]

70. During prosecution of the '708 and '270 patents, the applicants submitted an Information Disclosure Statement in which they cited and made of record an article by Joyce & Grindley, *Proc. Natl. Acad. Sci*. USA, vol. 80 pp.1830-1834 (1983) ("the 1983 Joyce & Grindley Publication"). [UF No. 109] *Stipulated Exhibit* No. 4. The 1983 Joyce & Grindley Publication describes the construction of a multicopy plasmid encoding the Klenow fragment of the *E. coli* DNA

[2] *See* '708 patent, col. 2, lines 23-29. ("However, it is an important feature of this invention that the cloned polA gene fragment contains essentially none of or at the most a portion of the activity of its natural promoter.")

polymerase I enzyme, which has DNA polymerase activity. However, it does not describe the construction of a multicopy plasmid encoding the complete *E. coli* DNA polymerase I enzyme. [UF No. 110, 111, 112]

71. Joyce & Grindley reported performing experiments with multicopy plasmids that encode the Klenow fragment of *E. coli* DNA polymerase I. They considered the Klenow fragment to be more attractive than the complete *E. coli* DNA polymerase I enzyme for the studies they wished to perform:

> Because the Klenow fragment retains the most interesting enzymatic activities of the parent molecule, but is only about two-thirds as large, we felt that it would make a much more attractive subject for structural studies. (1983 Joyce & Grindley Publication, page 1830, left column).

[UF No. 113, 114]

72. In performing their structural studies of the Klenow fragment, Joyce & Grindley did not need to construct a multicopy plasmid encoding the complete *E. coli* DNA polymerase I enzyme, or containing the complete *E. coli polA* gene coding region under control of a regulatable promoter. Nor did they need to solve the toxicity problem that the 1977 Kelley Publication described for the *E. coli polA* gene. [UF No. 115, 116, 117]

73. The 1983 Joyce & Grindley Publication reports that plasmids encoding the Klenow fragment do not present the toxicity problem described in the 1977 Kelley Publication for plasmids encoding the complete *E. coli* DNA polymerase I enzyme:

> Thus, although the wild-type *polA* gene is lethal on a multicopy plasmid, the separated activities corresponding to the Klenow fragment (polymerase and 3'-5' exonuclease) and the *polA1* amber fragment (5'-3' exonuclease) are not. (1983 Joyce & Grindley Publication, page 1832, left column.).

[UF No. 118]

74. The 1983 Joyce & Grindley Publication does not teach or suggest the construction of a multicopy plasmid containing the complete *polA* gene coding region under control of a regulatable promoter. However, Joyce & Grindley reported placing a gene coding sequence for a DNA Polymerase enzyme, the Klenow fragment, under the control of a foreign promoter that was conditionally controlled. *See* Davis Cross at 131-132.

75. Joyce & Grindley performed experiments that were much more relevant to the patents at issue than the Murray & Kelley and Remaut articles. Specifically, the testimony shows that Joyce & Grindley performed experimental manipulations of the *polA* gene coding region and of the natural promoter and provided one of skill in the art with protocols for how to perform such manipulations. Ex. 43 (Proposed Davis Testimony) ¶¶ 29-30. Joyce & Grindley also worked with multicopy plasmids that encoded enzymes with DNA polymerase activity. *Id.* ¶ 31. The '708 patent cites to Joyce & Grindley for those propositions at col. 1, line 61 – col. 2, line 8. Ex. 1. As opposed to the Murray & Kelly and Remaut articles, the Joyce & Grindley article described experimental results that were relevant to Dr. Minkley's work; thus Joyce & Grindley did more than just guess at possible solutions to noted problems. Joyce & Grindley was more material than Murray & Kelley and Remaut to the patents at issue.

76. During prosecution of the '745 patent, the Examiner cited the 1981 Remaut Publication and made it of record. [UF No. 119]

77. During prosecution of the '745 patent, in an Office Action dated July 16, 1993, the Examiner relied on the 1981 Remaut Publication, in combination with the 1997 Kelley Publication and a reference by Maniatis, as a basis for rejecting claims as obvious. The Examiner stated:

> Remaut et al. teach a method of transforming E. coli with a plasmid containing a regulatable promoter and of inducing said promoter. (Page 7, Office Action dated July 16, 1993).
>
> * * *
>
> Thus, in view of combined suggestions of Kelley et al. and Maniatis et al., it would have been obvious to have expressed the wild-type polA gene of Kelley et al. by transforming E. coli according to a method taught by Remaut et al. using a regulatable promoter taught by Maniatis et al. (*Id.*, page 8).

[UF No. 1210, 121, 122]

78. The applicants overcame the July 16, 1993 rejection during prosecution of the '745 patent by arguing, in an Amendment dated January 14, 1994, that the 1981 Remaut Publication "does not teach how to clone the *polA* gene or how to alter the promoter" and that "there was nothing to lead one skilled in the art from Kelley et al. to Remaut, et al." *See* Ex. 6.

79. The Examiner's citation to Remaut as a basis for initially rejecting claims of the

'745 patent, in 1993, shows that Remaut was also material to the '708 and '270 patents. However, the Remaut article was not highly material. As discussed, Remaut did not teach or suggest to one skilled in the art the techniques necessary to perform the process taught by the patents in suit. At most, Remaut provided a general hypothesis for how the toxicity problem might be overcome, without providing any specifics.

80. Because Remaut is of such limited materiality, it cannot be inferred that Dr. Minkley and his patent counsel deliberately withheld the 1981 Remaut Publication from the PTO during prosecution of the '708 and '270 patents in order more easily to obtain allowance of the claims being sought. Plaintiffs cited what they reasonably considered the most material prior art, the Joyce & Grindley article.

Alleged Inequitable Conduct re: the '708 and '270 Patents:
The Murray & Kelley Publication

81. In 1979, Professor Noreen Murray co-authored a scientific paper describing work with the *E. coli polA* gene. Murray & Kelley, *Molecular General Genetics* vol. 175, ¶. 77-87 (1979) ("the 1979 Murray & Kelley Publication"), Ex. 26. In discussion, the 1979 Murray & Kelley Publication stated:

> Amplification beyond the levels reported here must await the isolation of specific control mutations such as those demonstrated for the *lig* gene (Gottesman et al., 1973), or the fusion of the gene to another promoter either in lambda or a multicopy plasmid. However since we have not yet been able to demonstrate maintenance of the cloned *polA*+ allele in such a plasmid, the use of a multicopy plasmid may require a fusion which removes the polA promoter and places the gene under the control of a specific metabolic repressor or inducer. Until we develop an effective method of limiting transcription of the polA gene the lambda vector system will continue to be the most useful means of manipulating the gene.

Ex. 26 (1979 Murray & Kelly Publication, page 86, right column).

82. Murray & Kelley reported neither how to remove the *polA* promoter nor how subsequently to place the gene under the control of a specific metabolic repressor or inducer. RT at 380-381. Murray & Kelley indicated their inability to accomplish these tasks "[u]ntil we develop an effective method of limiting transcription of the *polA* gene . . . ." Ex. 26. Murray & Kelley thus only

communicated a desire to obtain such multicopy plasmids – not a teaching or suggestion how to obtain those plasmids. RT at 380, 401.

83. Dr. Minkley cited the 1979 Murray & Kelley Publication as a reference in the 1984 Minkley Publication in which he reported the work on which the patents-in-suit are based. [UF No. 142] However, he testified credibly that his reference related only to certain tables in the article listing the attributes of lambda phages, and that he did not read the entire article until October 2004. RT at 241-242. Defendants did not introduce clear and convincing evidence that plaintiffs were familiar with the allegedly material aspects of the Murray & Kelley publication during patent prosecution.

84. The 1979 Murray & Kelley Publication was never provided to the PTO or cited to the PTO in an Information Disclosure Statement in connection with the prosecution of the '708 or '270 patents. Nor was it listed in the "References Cited" section on the face of the '708 or '270 patents. [UF No. 143, 144, 145] The specification of the patents-in-suit does cite to the 1979 Murray & Kelley Publication in the section that describes the preferred embodiments, stating: "[t]he plasmid pMP5 was constructed as a derivative of the P_L expression vector pHUB2 (Bernard H. - U. Remault, E. Herschfield, M.V., Yanofsky, C. and Franklin, N. (1979) Gene 5, 59- 76) using the transducing phage NM825 (Murray, N.E. and Kelley, W. S. (1979) Mol. Gen. Genet. 175, 77 -87) as a source of polA+." (*See* '708 Patent at col. 5, lines 57-62). [UF No. 153]

85. The 1979 Murray & Kelley Publication was not material to prosecution of the '708 and '270 patents. Defendants did not introduce clear and convincing evidence that Dr. Minkley and his patent counsel deliberately withheld the Murray & Kelley Publication from the PTO during prosecution of the '708 and '270 patents in order more easily to obtain allowance of the claims being sought.

CONCLUSIONS OF LAW

Applicable Legal Rules

Inequitable conduct renders a patent unenforceable when "there is evidence of affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive." *Ulead Systems, Inc. v. Lex Computer &*

Management Corp., 351 F.3d 1139, 1144 (Fed. Cir. 2004). "Determination of inequitable conduct requires a two-step analysis." *PerSeptive Biosystems v. Pharmacia Biotech, Inc.*, 225 F.3d 1315, 1318 (Fed. Cir. 2000). "First, the trial court must determine whether the conduct meets a threshold level of materiality." *Id.* "The trial court must then also determine whether the evidence shows a threshold level of intent to mislead the PTO." *Id.* at 1319. Inequitable conduct must be established by clear and convincing evidence. *Ulead Systems*, 351 F.3d at 1144.

Information is "material" where "there is a substantial likelihood that a reasonable examiner would have considered the information important in deciding whether to allow the application to issue as a patent." *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1179 (Fed.Cir. 1995). "The more material the conduct, the less evidence of intent will be required in order to find that inequitable conduct has occurred." *PerSeptive Biosystems*, 225 F.3d at 1319.

"In evaluating materiality, this court has consistently referred to the standard set forth in PTO Rule 56." *Purdue Pharma, Pharma L.P. v. Endo Pharmaceuticals, Inc.*, 410 F.3d 690, 696 (Fed. Cir. 2005) (citing *Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd.*, 394 F.3d 1348, 1352 (Fed. Cir. 2005)). From August, 1984 (when the '638 Application was filed) until March, 1992, Rule 56 provided, in pertinent part:

> (a) A duty of candor and good faith towards the Patent and Trademark Office rests on the inventor, on each attorney or agent who prepares or prosecutes the application and on every other individual who is substantively involved in the preparation or prosecution of the application and is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application. All such individuals have a duty to disclose to the Office information they are aware of which is material to examination of the application. Such information is material where there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent.

37 C.F.R. § 1.56 (1984).

With effect from March 16, 1992, Rule 56 was amended to provide, in pertinent part:

> (b) [I]nformation is material to patentability when it is not cumulative to information already of record or being made of record in the application, and
>
> (1) It establishes, by itself or in combination with other information, a *prima facie* case of unpatentability of a claim; or
>
> (2) It refutes, or is inconsistent with, a position the applicant takes in:

(i) Opposing an argument of unpatentability relied on by the Office, or

(ii) Asserting an argument of patentability.

37 C.F.R. § 1.56 (1992); 57 Fed. Reg. 2021 *et seq*. (Jan. 17, 1992).

Material information includes documents and testimony from patent litigations. At all times relevant to the Bambara Declaration, the Manual of Patent Examining Procedure (MPEP) provided as follows, in relevant part:

> Where the subject matter for which a patent is being sought is or has been involved in litigation, the existence of such litigation and any other material information arising therefrom must be brought to the attention of the Patent and Trademark Office. . . . Another example of such material information is any assertion that is made during litigation that is *contradictory to assertions made to the examiner*. Such information might arise during litigation during, for example, pleadings, admissions, discovery including interrogatories, depositions, and other documents and testimony.

MPEP § 2001.06(c) (7th ed., July, 1998) (citation omitted) (emphasis added); see *Critikon*, 120 F.3d at 1258 (holding patents unenforceable where applicants failed to comply with their duty under MPEP § 2001.06(c)).

In determining whether a prior art reference renders claimed subject matter obvious, "the question . . . is not merely what the references expressly teach but what they would have suggested to one of ordinary skill in the art at the time the invention was made." *Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989); *accord May v. American Southwest Waterbed Distributors, Inc.*, 715 F.2d 876, 884 (Fed. Cir. 1983) ("it is not merely what prior art teaches, but what it suggests to one of ordinary skill in the art at the time of invention").

"[I]ntent as an essential predicate to patent unenforceability does not mean that the inventor intended to do what he did in patent prosecution; it means that the inventor intended to deceive or mislead the examiner into granting the patent." *Therma-Tru Corp. v. Peachtree Doors Inc.*, 44 F.3d 988, 995-96 (Fed. Cir. 1995); *see also Speedplay, Inc. v. Bebop, Inc.*, 211 F.3d 1245, 1259 (Fed. Cir. 2000). "[I]ntent to mislead does not require direct evidence, and is typically inferred from the facts." *Bristol-Myers Squibb Co. v. Rhone-Poulenec Rorer, Inc.*, 326 F.3d 1226, 1239 (Fed. Cir. 2003). An applicant's intent to mislead the Examiner "need not be proven by direct evidence; it is most often proven by a showing of acts, the natural consequence of which are presumably intended by the actor."

Semiconductor Energy Lab. Co. v. Samsung Elec. Co., 204 F.3d 1368, 1374-75 (Fed. Cir. 2000) (*quoting Molins plc v Textron, Inc.*, 48 F.3d 1172, 1180 (Fed. Cir. 1995)).

"[W]here withheld information is material and the patentee knew or should have known of that materiality, he or she can expect to have great difficulty in establishing subjective good faith sufficient or overcome an inference of intent to mislead." *Bristol-Myers*, 326 F.3d at 1239. "[P]atentee facing a high level of materiality and clear proof that it knew or should have known of that materiality, can expect to find it difficult to establish 'subjective good faith' sufficient to prevent the drawing of an inference of intent to mislead. A mere denial of intent to mislead (which would defeat every effort to establish inequitable conduct) will not suffice in such circumstances." *Critikon Inc. v. Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253, 1257 (Fed. Cir. 1997). Where the patentee has not proffered a credible explanation for the nondisclosure of a material reference, "an inference of deceptive intent may fairly be drawn in the absence of such an explanation." *Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs. Ltd.*, 394 F.3d 1348, 1354 (Fed. Cir. 2005).

To establish inequitable conduct based on failure to disclose prior art, the party "must offer clear and convincing proof of: (1) prior art or information that is material; (2) knowledge chargeable to applicant of that prior art or information and of its materiality; and (3) failure of the applicant to disclose the art or information resulting from an intent to mislead the PTO." *FMC Corp. v. Manitowoc Co.*, 835 F.2d 1411, 1415 (Fed. Cir. 1987); *see also Elk Corp. v. GAF Building Materials Corp.*, 168 F.3d 28, 30 (Fed. Cir. 1999); *Mentor Graphics Corp. v. Quickturn Design Systems, Inc.*, 2003 U.S. Dist. LEXIS 16197 (N.D. Cal. 2003).

Proof of inequitable conduct may be rebutted by showing that: a) the prior art was not material; b) if the prior art was material, a showing that the applicant did not know of the art; c) if the applicant did know of the art a showing that the applicant did not know of its materiality; or d) a showing that the applicant's failure to disclose the art did not result from an intent to mislead the PTO. *Elk Corp.*, 168 F.3d at 30. If an applicant fails to disclose a material prior art reference, the failure to disclose will not support a finding of inequitable conduct if the reference is "simply cumulative to other references, i.e., if the reference teaches no more than what a reasonable examiner would consider to be taught by the prior art already before the PTO." *Regents of the University of California v. Eli Lilly and Company*, 119

F.3d 1559, 1574-75 (Fed. Cir. 1997).

After threshold findings of materiality and intent have been established by clear and convincing evidence, the court must weigh them to determine if equity warrants a finding of inequitable conduct. *Ulead Systems, Inc.*, 351 F.3d at 1144.

"In the context of an inequitable conduct determination, the 'applicant' includes anyone under a duty to disclose material information to the PTO pursuant to 37 C.F.R. § 1.56, namely: the inventor, the prosecuting attorney or agent, and anyone associated with the inventor or the assignee who is substantively involved in the preparation or prosecution of the application." *Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd.*, 394 F.3d 1348, 1351 n.3 (Fed. Cir. 2005) (citing *Molins*, 48 F.3d at 1178 n.6); *accord FMC Corp. v. Mainitowoc Co.*, 835 F.2d 1411, 1415 n.8 (Fed. Cir. 1987) ("the knowledge and actions of the applicant's attorney are chargeable to the applicant.").

Alleged Inequitable Conduct re '745 Patent Prosecution: The Bambara Declaration

This Court has found that the Bambara Declaration was material to patentability of certain claims of the '745 Patent under *Eli Lilly*, as was reflected in the Court's reliance on the Bambara Declaration in holding the '745 Patent invalid in 2003. However, the Court also concludes that the Bambara Declaration would have been of limited materiality to the '745 Patent Examiner. The facts contained in the Bambara Declaration were known to those skilled in the art at the time; and there is no evidence that plaintiffs misrepresented these facts to the Examiner. The opinions contained in the relevant portions of the Bambara Declaration were summarized in the Court's '270 Patent Invalidity Order, which plaintiffs provided to the Examiner. Even without the Bambara Declaration, therefore, the Examiner was aware of the argument that the Bambara Declaration supported. The Court concludes that the Bambara Declaration was material, but not highly so.

Furthermore, defendants have not established by clear and convincing evidence that, prior to 2003, plaintiffs knew how material the Bambara Declaration was. The parties referred to the Bambara Declaration in their briefs and oral argument on the '270 Patent, in 1999, but the Court's Order on that issue did not cite the Bambara Declaration in relation to the *Eli Lilly* issue. It was not until the 2003

summary judgment order in the second action that this Court accepted defendants' *Eli Lilly* argument based on the Bambara Declaration.

Finally, defendants have not established by clear and convincing evidence that plaintiffs intended to deceive or mislead the examiner into granting the '745 patent by not submitting the Bambara Declaration. Because of the low materiality of the Declaration, and the scant evidence that plaintiffs realized its materiality in 1999, the Court cannot infer intent. Moreover, plaintiffs presented a convincing explanation for not providing the Bambara Declaration to the Examiner. In determining which documents in a large litigation record should be produced to an examiner, the prosecuting party must draw the line somewhere. As Bjorge testified, the PTO wants neither too little, nor too much, litigation material. Presenting too many documents creates the risk of being accused of burying material information. In the case of the Bambara Declaration, plaintiffs drew the line in the wrong place. The evidence suggests, however, that they did so inadvertently, not intentionally.

The Court concludes that defendants have not proved by clear and convincing evidence that plaintiffs committed inequitable conduct by failing to present the Bambara Declaration to the PTO in the course of the '745 patent prosecution.

Alleged Inequitable Conduct re: the '708 and '270 Patents:
The Minkley Declaration And The March 15, 1990 Amendment

Defendants contend that Dr. Minkley's 1990 declaration falsely claimed that he had placed a recombinant plasmid providing for Nick-translation activity in a yeast host system. Dr. Minkley stated in his declaration:

> At least as early as December 14, 1983, I had placed a recombinant plasmid providing for Nick-translation activity in a bacterial or yeast host system. Next, I allowed such a bacterial or yeast host system to reproduce. I then obtained an enzyme for Nick-translation activity from the host systems that reproduced.

[UF No. 58].

It is uncontested that Dr. Minkley never performed the activity described above in a yeast host system. The declaration was designed to overcome an obviousness rejection by the Examiner based on an article by Spanos and Sedgwick. If Dr. Minkley had performed the same work as the Spanos article before the publication of the article, then a declaration to that effect would overcome an obviousness

rejection. *See In re Stempel*, 241 F.2d 755, 759 (C.C.P.A.1957). Defendants argue that Dr. Minkley misstated his previous work in order to overcome the rejection.

The Court concludes that defendants have not established by clear and convincing evidence that the Minkley Declaration would lead a reasonable examiner to conclude that Minkley had completed experiments in both bacteria and yeast hosts. First, the plain language of the Declaration is not untrue. Minkley had "as early as December 14, 1983, . . . placed a recombinant plasmid providing for Nick-translation activity in a bacterial *or* yeast host system." (emphasis added).

In response, defendants argue that while the Minkley Declaration was not, on its face, untrue, it was intentionally worded to create a misperception in the mind of the Examiner. As such, defendants argue, this case is analogous to *Purdue Pharma L.P. v. Endo Pharmaceuticals, Inc.*, 410 F.3d 690 (Fed. Cir. 2005). In *Purdue*, the Federal Circuit held that an applicant failed to disclose material information when it made statements to the PTO which, while perhaps technically correct, suggested that certain scientific experiments had been conducted when they had not been. In *Purdue*, the patent applicant repeatedly communicated to the PTO its "surprising discovery" that its invention (controlled release oxycodone) controlled pain in 90% of patients over a four-fold range of dosages, where prior art opiods required an eight-fold range of dosages. *Id*. at 696. Purdue had not performed scientific experiments establishing the "surprising discovery" of a four-fold dosage range; the "discovery" was merely an insight of Purdue's inventor, Dr. Kaiko. *Id*. at 696-97. The court held: "While Purdue never expressly stated that the discovery of the four-fold dosage range was based on the results of clinical studies, that conclusion was clearly to be inferred from the language used by Purdue in both the patents and prosecution history." *Id*. at 698.

As the court explained in more detail:

> For example, Purdue a number of times during prosecution referred to the four-fold dosage range as a 'result,' implying that clinical results had been obtained. Purdue also frequently noted the 'clinical significance' of its discovery, sometimes, as in the Kaiko attachment, in close proximity to a description of the clinical studies performed by Purdue, again suggesting the discovery was supported by experimental results. In addition, Purdue continually compared the dosage range of controlled release oxycodone to that of other opioid analgesics in concise, quantitative terms (e.g., four-fold vs. eight-fold for approximately 90% of patients). In the absence of any statements indicating the true origin of its 'surprising discovery,' Purdue's arguments to the PTO provide enough of a suggestion that clinical trials had been performed that failure to tell the PTO the discovery was based on Dr. Kaiko's insight and not scientific proof was a

failure to disclose material information.

Id. at 698.

Here, a reasonable Examiner could not "clearly . . . infer[] from the language used by" Minkley that he had conducted both types of experiments. The relevant portion of the Minkley Declaration, standing alone, would not lead a reasonable Examiner to infer that Minkley had performed on both bacteria and yeast hosts. This conclusion is bolstered by the fact that the Examiner in this case, after reviewing the Minkley Declaration and the Amendment, determined that Minkley had not performed on yeast hosts. [UF No. 70].

Furthermore, the Minkley Declaration, immediately after the "bacterial or yeast host system" sentence, states: "An article, see E.G. Minkley et al. J. Biol. Chem., 259(16) 10386 (1984), copy attached, describing the same was submitted for publication on December 14, 1983." The cited publication describes only Minkley's work on the *E. Coli* bacterial host. This explicit reference is thus sufficient to dispel any implication that Minkley intended to deceive the Examiner into believing he had worked on anything more than *E. Coli* bacterial host systems.

The Court concludes that the "bacterial or yeast host system" sentence would not have led a reasonable Examiner to infer that Minkley had worked in both systems prior to Spanos, and is therefore immaterial. Furthermore, there is insufficient evidence to support a conclusion that Minkley intended to mislead the Examiner. Defendants have not presented clear and convincing evidence that the Minkley Declaration and the March 15, 1990 Amendment constituted "affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive." *Ulead Systems*, 351 F.3d at 1144. Plaintiffs therefore did not commit inequitable conduct by submitting the Minkley Declaration and the Amendment, and the '708 and '270 patents are not unenforceable on that account.

Alleged Inequitable Conduct re: the '708 and '270 Patents: The Remaut Publication

Defendants contend that a reasonable examiner would have considered the Remaut Publication relevant to the patents-in-suit and that plaintiffs' failure to present it to the Examiner constitutes

inequitable conduct.

Plaintiffs' patents addressed the problem of constructing a multicopy plasmid containing the gene that encodes DNA polymerase I, in light of the lethality of the pol I enzyme to bacterial host cells when expressed at elevated levels. The patents in suit describe a solution to this problem: using a regulatable promoter to replace the natural promoter, thereby controlling creation of DNA polymerase in a multicopy plasmid. Defendants argue that the Remaut article also addresses the toxicity problem discussed in the plaintiffs' patents-in-suit, and suggests the solution that plaintiffs' patents describe. The relevant portion of the Remaut article states that "[t]he ability to control transcription may be a prerequisite for cloning of genes whose continuous expression is detrimental to the cell." Ex. 22 at 90.

The Court has found that the Remaut Publication was material, as evidenced by the Examiner's reliance on it in initially rejecting the '745 Patent. However, Remaut was of limited materiality: it did not work with *polA* at all, nor any toxic gene product, and offered only a vague suggestion ("the ability to control transcription *may be* a prerequisite") as a potential solution to the lethality problem. It provided no procedures or plasmid constructs by which one of skill in the art could accomplish the "ability to control transcription." It offered no teaching to the skilled practitioner regarding how to place the *polA* gene coding region onto a multicopy plasmid or concerning the importance of reducing the activity of the natural promoter. Nor does it teach manipulating the natural promoter of the *polA* gene independent of the gene coding region.

Moreover, defendants have not established by clear and convincing evidence that plaintiffs had reviewed the entire Remaut Publication prior to the relevant time periods. Minkley testified that he recalled reviewing only those discrete portions of the Remaut article that he used in his research and did not remember using or reviewing the portion defendants now assert was material; the Court found this testimony credible.

Because of its very limited materiality, and the scarce evidence that plaintiffs knew of the portion of the Remaut article at issue, the Court cannot infer that plaintiffs intended to deceive the Examiner. There is no direct evidence of intent. The Court therefore concludes that Dr. Minkley and his patent counsel did not commit inequitable conduct during prosecution of the '708 and '270 patents by withholding the 1981 Remaut Publication. *See Ulead Systems*, 351 F.3d at 1144.

Alleged Inequitable Conduct re: the '708 and '270 Patents:
The Murray & Kelley Publication

As with the Remaut article, defendants contend that the Murray & Kelley article is material because it suggests the solution to the toxicity problem described by the patents at issue. The Court disagrees. As discussed, Murray & Kelley reports neither how to remove the *polA* promoter nor how to subsequently place the gene under the control of a specific metabolic repressor or inducer. Murray & Kelley only communicates a desire to obtain such multicopy plasmids – it does not teach how to obtain those plasmids. RT at 380. The 1979 Murray & Kelley Publication therefore was not material to patentability of claims of the '708 and '270 patents.

Furthermore, plaintiffs cited the Murray & Kelley article in the patent specifications. Bjorge credibly testified that patent examiners are taught to, and generally do, review all references cited in a patent application. The Murray & Kelley publication was therefore not withheld from the PTO.

Finally, there is no evidence that plaintiffs deliberately withheld the Murray & Kelley article in order to mislead the Examiner. The Court therefore concludes that Dr. Minkley and his patent counsel did not commit inequitable conduct during prosecution of the '708 and '270 patents by withholding the 1979 Murray & Kelley Publication.

In sum, the Court concludes that defendants have failed to prove by clear and convincing evidence that plaintiffs committed inequitable conduct during prosecution of any of the patents in suit.

IT IS SO ORDERED.

Dated: March 22, 2007

Susan Illston

SUSAN ILLSTON
United States District Judge